

**REMARKS**

Applicants thank the Examiner for withdrawing some rejections from the previous office action and for providing further guidance on the how to improve the claims. In the current Amendment and Response, Applicants are providing further amendments to the set of claims in order to place the claims in condition for allowance. Applicants respectfully ask the Examiner to enter these Amendments After Final Rejection. Applicants have canceled claims 69-75 and 92, amended claims 76- 80, 83-89 and 93 and have added new dependent claims 94-99. Support for new dependent claims 94-99 can be found in the specification at, for example, page 14, line 28-30, page 15, lines 18-21 and the claims as filed. Upon entry of the amendment, claims 76-91 and 93-99 will be pending.

In addition, Applicants have amended a figure legend in the Specification to facilitate practitioners' referral to the sequences presented in the corresponding figure. Applicants also have provided a new Sequence Listing to correct the identifiers for the sequences presented therein. Specifically, for the sequences representing cytoplasmic domains of integrin subunits other than the GP IIIa integrin  $\beta 3$  (SEQ ID NO:1), Applicants have replaced "GP IIIa" with "integrin."

In the following paragraphs, Applicants respond to the objections and rejections of the Final Office action mailed March 23, 2004.

**Objection to Claim 93**

The Examiner objected to claim 93 due to inaccurate identification of claim steps. Claim 93 has been amended to replace the identifiers "c" and "d" with "a)" and "b)." Applicants respectfully ask the Examiner to withdraw this objection.

**Rejection of Claims Under 35 U.S.C. §112, First Paragraph**

Rejections of claims under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the relevant art to make and/or use the invention have been maintained.

First, Applicants would like to clarify the relevant claim numbers referred to for the rejections. On page 3, paragraph 2 of the Office Action, the Examiner refers to claims 69-78 as reciting a "chimeric" mouse as a result of the previous amendment. However, Applicants note that "chimeric" was only recited in claims 69-75. Clarification that the rejection in this paragraph is limited to claims 69-75 and does not include claims 76-78 is requested. Second, on page 3, paragraph 3 of the Office Action, the Examiner refers to claims 76-78 as having a phenotype in the first line, but on the fourth line, the Examiner refers to claims 69-75 and 75-92 when rejecting for lack of phenotype. It appears in the second case, that due to

the Examiner further referring to claims 69-73 on this line that the actual rejection in this paragraph applies to claims 69-73 and not claims 75-92. Confirmation of this conclusion is requested.

In regard to the rejection in paragraphs 2 and 3 of page 3-4 of the Office Action, if Applicants' interpretation of the applicable claims is correct, cancellation herein of claims 69-75 obviates these rejections. In view of this amendment, Applicants respectfully ask that these rejections be withdrawn.

Applicants also would like to add to the Examiner's understanding of the Law exhibit (submitted in a Response filed January 2, 2002). The Examiner states, on page 4 of the Office Action, that the Law Exhibit provides teachings on mice homozygous for the mutant  $\beta 3$  gene. Applicants herein draw the Examiner's attention to where Law Exhibit also provides teachings for mice heterozygous for the mutant  $\beta 3$  gene. For example, at page 809, lines 9-10, the Law Exhibit discloses that heterozygous mice have an intermediate response between wild type and homozygous mutant mice in a thrombin assay and in a platelet aggregation assay. In another example, Figure 4b on page 810 of the Law Exhibit depicts an intermediate response by heterozygous mice. Thus, the Law Exhibit provides teachings on mice homozygous and mice heterozygous for the mutant  $\beta 3$  gene.

In regard to the further rejection of claims 79-92 for lack of a phenotype on page 5 of the Office Action, Applicants first would like to clarify to which claims this rejection refers. Applicants note that claim 82 is dependent on claim 76, which the Examiner, on page 3, line 1 of paragraph 3, concedes does provide a phenotype. Therefore, Applicant requests confirmation that this rejection applies only to claims 79-81 and 83-92. If Applicants are correct in their conclusion that this rejection refers to claims 79-81 and 83-92, then in response, Applicants have canceled claim 92 and have amended claims 79, 83, and 87 (claims 80, 81, 84-86, and 88-91 dependent thereon) to recite the phenotype in claim 76. In view of these amendments and remarks, Applicants ask that this rejection be withdrawn.

Claims 76-78 and 93 were later rejected on the basis that the application provides guidance for a phenotype exemplified by platelets, but not for any cells. Applicants respectfully traverse this rejection, because the phenotype (e.g. an alteration in phosphorylation of GP IIIa ( $\beta 3$  integrin)) provided by the specification and the claims can be measured on that protein identified in any cell where it is expressed (e.g. the endothelial cell or the neutrophil described on page 16, lines 9 and 11). However, in the interest of obtaining allowance of the claims, Applicants have included in claims 76 (claims 77-78 dependent thereon) and 79, 83 and 87, the limitation that the platelets from the claimed mouse have the claimed phenotype. In view of these amendments, Applicants respectfully ask that this rejection be withdrawn.

#### Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

Claim 69 was rejected under 35 U.S.C. §112, second paragraph for being "vague and indefinite." Applicants have canceled claim 69 and dependent claims 70-75 and 92. In view of these amendments, Applicants respectfully ask that this rejection be withdrawn.

Claims 70, 73, 77, 80, 84 and 89 were rejected under 35 U.S.C. §112, second paragraph for being “vague and indefinite.” In this rejection, the Examiner finds the claims unclear in their recitation of tyrosine residues 747 or 759 and the lack of a reference point for the sequence. The Examiner was not persuaded by Applicants’ prior remarks on how the specification provides reference points. In response, Applicants have canceled claims 70 and 73 and have amended claims 77, 80, 84 and 89 to recite that the mutations in the gene will change one or both of the cytoplasmic tyrosine residues portrayed in the GP IIIa ( $\beta$ 3 integrin) sequence provided in Figure 2 and SEQ ID NO:1. Support for this amendment can be found in the specification at, for example, the Figure 2 legend and page 11, lines 4-5. The description of this figure clearly shows reference points from the beginning to the end of the cytoplasmic domain of this protein. The sequence in this figure also provides neighboring residue information for one skilled in the art to align a mouse  $\beta$ 3 integrin sequence and clearly identify the tyrosine residue(s) to mutate. In view of these amendments and remarks, Applicants respectfully ask that this rejection be withdrawn.

Claim 76 was rejected under 35 U.S.C. §112, second paragraph for being “vague and indefinite.” In this rejection, the Examiner finds the claim unclear in its apparent comparison between a mouse and a protein. In response, Applicants have amended claim 76 (claims 77 and 78 dependent thereon) and claims 79, 83 and 87 to clarify that both a transgenic mouse and a wild type mouse are contributing platelets from which the phosphorylation of GP IIIa protein is being measured. In view of these amendments and remarks, Applicants respectfully ask that this rejection be withdrawn.

Claim 83 was rejected under 35 U.S.C. §112, second paragraph for being incomplete. The Examiner finds that the generation of blastocysts fails to relate to the preamble, which is a method for preparing a transgenic mouse. In response, Applicants have amended claim 83 to clarify the mouse claimed in the preamble, have amended step c) and added step d) to recite the steps to produce the mouse recited in the preamble as amended. The recitation of the generation of chimeric mice from blastocysts in step c) is a step known in the art and described in the specification (e.g. at page 21, lines 27-29). The further step of mating the chimeric mouse generates the mouse claimed in the preamble. In view of these amendments and remarks, Applicants believe that claim 83 is complete and ask that this rejection be withdrawn.

Claim 92 was rejected under 35 U.S.C. §112, second paragraph for having insufficient antecedent basis for the limitation “transgenic.” Claim 92 is canceled herein, so this rejection should be withdrawn.

Claim 93 was rejected under 35 U.S.C. §112, second paragraph for being incomplete. The Examiner requested that the step of determining the effect of the biological response relate to the biological response in the preamble. Applicants have incorporated into the step the biological response found in the preamble. In view of this amendment, Applicants request that this rejection be withdrawn.

Rejection of Claims Under 35 U.S.C. §102

The rejection of claim 75 under 35 U.S.C. §102 was maintained. Applicants have canceled claim 75 and ask that this rejection be withdrawn.

CONCLUSIONS

Applicants respectfully request that the Examiner enter these amendments after final rejection because, in view of these amendments and remarks, Applicants respectfully submit that the objections to and rejections of claims 69-93 under 35 U.S.C. §§ 112 and 102 are herein overcome and that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned. If the Examiner disapproves of Applicants' amendments and remarks in this response, Applicants request a prompt mailing of an Advisory Action to that effect.

This paper is being filed timely within two months of the mailing date of the final action. No extensions of time are required. In the event any extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Respectfully submitted,

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MILLENNIUM PHARMACEUTICALS, INC.

By Tracy M. Sioussat  
Tracy M. Sioussat, Ph.D.  
Registration No. 50,609  
40 Landsdowne Street  
Cambridge, MA 02139  
Telephone - 617-374-7679  
Facsimile - 617-551-8820